2011 Annual Report: Locking out HIV

News at CIRM:

Locking Out HIV

Two years ago, Jeff Sheehy sounded frustrated as he talked about HIV. Yes, antiretroviral therapy launched a revolution in care. Yes, it kept people alive. But it was not a cure. Far from it. Besides the downsides of sometimes nasty side effects and significant cost, people with HIV were developing heart disease, their livers and kidneys showed damage. Even those with well-controlled infections died 10 years earlier than people without HIV.

By 2010, the elation that had originally greeted effective antiretroviral therapy was supplanted by "a new realism, and almost a kind of grit-your-teeth-and-let's-just-plug-on spirit. That's kind of where we've been," Sheehy said in 2010.

Today, Sheehy, an HIV patient advocate and a CIRM board member, sounds almost ebullient, and certainly positive about accumulating research showing progress toward more effective treatments for HIV, and even what people are calling a "functional cure."

"I'm incredibly optimistic," Sheehy says. "I don't think we're going to get here tomorrow, but I think the train has left the station to get there. The whole dialog has been completely upended, and CIRM has been at the cutting edge."

That growing optimism originates with a single man–known as the Berlin patient–who received a functional cure for his HIV infection. The bone marrow transplant that cured him isn't an option for all people, but the science underlying his therapy forms the basis for two teams of CIRM-funded researchers who are translating that success into a more broadly applicable therapy. Both aim to begin human trials in 2014.

Locking Out HIV

The story for what might become a cure for HIV infection began in the mid-1990s, when researchers learned that most human immunodeficiency virus made its way into cells through a protein on the cell surface called CCR5. If someone has mutations in both CCR5 genes, HIV is locked out; about 1 percent of Caucasians have two copies of this mutation and are resistant to HIV infection.

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That interesting tidbit graduated to a promising find when a German physician gave an HIV-positive leukemia patient a bone marrow transplant from a donor with two copies of the CCR5 mutation. The bone marrow transplant cured his leukemia; the mutated CCR5 eradicated his HIV. That man was known as the Berlin patient until 2010, when the American named Timothy Ray Brown went public. Today, he remains HIV free.

Brown's story is an inspiration, but it's not a cure for everyone. There aren't enough bone marrow donors with the CCR5 mutation to carry out the transplant for all people infected with HIV. Instead, the CIRM teams are working to create that mutation in patient's own cells.

An Obvious Solution

Even before the Berlin patient, researchers and biotech companies had their eye on CCR5 as an avenue for treating HIV infection. Among those scientists was Paula Cannon, today an associate professor in molecular microbiology & immunology at the University of Southern California. She was at a scientific conference when a scientist from Richmond-based Sangamo BioSciences, Inc. discussed the company's work in zinc-finger nuclease enzymes capable of targeting a gene and disrupting it.

"I actually woke up in this very boring meeting," Cannon says. "This is really something. I contacted them about getting involved."

"I never really ever thought too much about how my research would affect therapy and treatment," she says. "I felt a very long way

from that." Her science was about the nitty-gritty mechanisms of HIV, not about curing patients.

Then she engaged what she calls her "magical graduate student," Nathalia Holt.

"She was the wonderful combination of all this ability and all this enthusiasm and just enough naivety not to realize what she was getting into." Holt would try zinc-finger technology against HIV.

This could only happen in California. if not here then where else?

Cannon's team first used zinc-finger nucleases to alter the CCR5 gene in human blood-forming stem cells, then gave those altered cells to mice that lacked an effective immune system. Those cells colonized the bone marrow of the mice and created a new blood system replete with the mutated CCR5. That mutation closed the door on HIV. Exposed to HIV, the mice beat it back.

When Cannon published her work in *Nature Biotechnology* in July 2010 it received widespread attention. The fact that scientists could create a mutation that blocks HIV was the first sign that the Berlin patient's story really could be replicated, at least in mice.

But Cannon was not surprised.

"The fact that it worked, it was like the 'Duh!' moment. It was the most unremarkable thing," Cannon says. "I wasn't quite prepared for how exciting people thought the results were."

Cannon and Sangamo scientists are part of a $14.5 million CIRM-funded team led by John Zaia at City of Hope. They are working to translate Cannon's success in mice to people. Unlike Cannon, whose original interest was in the fundamental part of research, Zaia has a long-standing goal of treating HIV infection. He led some of the earliest studies attempting to modify the blood system to thwart infection.

Although his early work didn't succeed, Loring Leeds, an HIV patient who participated in an early trial, remains hopeful. "I'm very optimistic, I have to say. I just believe there is so much good work being done right now. I have to believe somebody will crack this, one way or the other."

The people who will crack that problem might be the Zaia/Cannon/Sangamo team, or it might be another CIRM team, this one led by Irvin Chen, director of the UCLA AIDS Institute. Like Zaia's team, he intends to alter the patient's own blood-forming stem cells so that they fail to produce functional CCR5, and combine it with another method of blocking a second HIV entry into the cell, then reintroduce those cells into the patient. The resulting blood system, lacking an entry into the cells, should thwart HIV infection.

The difference is that where Zaia's team is harnessing Sangamo's zinc-finger technology, Chen's team is working with a molecule called a short hairpin RNA. Rather than mutating the CCR5 gene, this molecule prevents the CCR5 gene that's there from making its protein. No CCR5 protein, no HIV in the cell. It's a different approach but with ultimately the same end goal.

Work Remaining

Despite progress by both teams, Cannon warns that there is still a lot of effort remaining. For example, the cells must be screened to make sure they don't have side effects that could harm people Then there's the issues of scale up – moving from dealing with a few mouse cells, to recovering human blood cells and altering those cells, which is multi-fold more difficult in humans.

But, Sangamo President and CEO Edward Lanphier is bullish.

"We are well down the road from biological proof of concept and animal model testing. We are very much in the stage of focusing on issues regarding bringing this to clinic, which is the goal of the (CIRM) grant." It's an optimism not even the researchers can resist.

"This could only happen in California," Cannon says. "I really think it's the only place on the planet where we're doing this important research. We have the right amount of resources, with the stem cell funding. We believe in technology–we have Silicon Valley. We believe in biotech. We've made a huge amount of progress.

"If not here, where else?"